

SEQUENCE LISTING

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<120> METALLOPROTEASE ACTIVATION OF MYOSTATIN, AND METHODS OF MODULATING MYOSTATIN ACTIVITY

<130> JHU1800-3

<150> US 60/486,863

<151> 2003-07-10

<150> US 60/439,164

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<150> US 60/411,133

<151> 2002-09-16

<160> 23

<170> PatentIn version 3.1

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Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val	
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Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His	
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Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr	
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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys	
245 250 255	
gta aca gac aca cca aaa aga tcc aga agg gat ttt ggt ctt gac tgt	874
Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys	
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val	
275 280 285	
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Leu Pro Lys Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val
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Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
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Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
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Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu
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Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val
 195 200 205

Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
 210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
 225 230 235 240

Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Lys
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
 275 280 285

Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
 290 295 300

Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
 305 310 315 320

Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
 325 330 335

Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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Val Asp Arg Cys Gly Cys Ser
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Val	Ala	Gly	Pro	Val	Asp	Leu	Asn	Glu	Asn	Ser	Glu	Gln	Lys	Glu	Asn	
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gtg	gaa	aaa	gag	ggg	ctg	tgt	aat	gca	tgt	ttg	tgg	agg	gaa	aac	act	144
Val	Glu	Lys	Glu	Gly	Leu	Cys	Asn	Ala	Cys	Leu	Trp	Arg	Glu	Asn	Thr	
		35					40					45				
aca	tcg	tca	aga	cta	gaa	gcc	ata	aaa	atc	caa	atc	ctc	agt	aaa	ctt	192
Thr	Ser	Ser	Arg	Leu	Glu	Ala	Ile	Lys	Ile	Gln	Ile	Leu	Ser	Lys	Leu	
	50					55					60					
cgc	ctg	gaa	aca	gct	cct	aac	atc	agc	aaa	gat	gct	atc	aga	caa	ctt	240
Arg	Leu	Glu	Thr	Ala	Pro	Asn	Ile	Ser	Lys	Asp	Ala	Ile	Arg	Gln	Leu	
65					70					75					80	
ttg	ccc	aag	gct	cct	cca	ctc	ctg	gaa	ctg	att	gat	cag	ttc	gat	gtc	288
Leu	Pro	Lys	Ala	Pro	Pro	Leu	Leu	Glu	Leu	Ile	Asp	Gln	Phe	Asp	Val	
				85				90						95		
cag	aga	gat	gcc	agc	agt	gac	ggc	tcc	ttg	gaa	gac	gat	gac	tac	cac	336
Gln	Arg	Asp	Ala	Ser	Ser	Asp	Gly	Ser	Leu	Glu	Asp	Asp	Asp	Tyr	His	
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gcc	agg	acg	gaa	acg	gtc	att	acc	atg	ccc	acg	gag	tct	gat	ctt	cta	384
Ala	Arg	Thr	Glu	Thr	Val	Ile	Thr	Met	Pro	Thr	Glu	Ser	Asp	Leu	Leu	
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acg	caa	gtg	gaa	gga	aaa	ccc	aaa	tgt	tgc	ttc	ttt	aaa	ttt	agc	tct	432
Thr	Gln	Val	Glu	Gly	Lys	Pro	Lys	Cys	Cys	Phe	Phe	Lys	Phe	Ser	Ser	
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Lys	Ile	Gln	Tyr	Asn	Lys	Leu	Val	Lys	Ala	Gln	Leu	Trp	Ile	Tyr	Leu	
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Arg	Pro	Val	Lys	Thr	Pro	Ala	Thr	Val	Phe	Val	Gln	Ile	Leu	Arg	Leu	
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atc	aaa	ccc	atg	aaa	gac	ggc	aca	agg	tat	act	gga	atc	cga	tct	ctg	576
Ile	Lys	Pro	Met	Lys	Asp	Gly	Thr	Arg	Tyr	Thr	Gly	Ile	Arg	Ser	Leu	
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Lys	Thr	Val	Leu	Gln	Asn	Trp	Leu	Lys	Gln	Pro	Glu	Ser	Asn	Leu	Gly	
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Ile	Glu	Ile	Lys	Ala	Leu	Asp	Glu	Asn	Gly	His	Asp	Leu	Ala	Val	Thr	
225					230				235						240	
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val				
	275	280	285	
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Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr				
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys				
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala				
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Val Glu Lys Glu Gly Leu Cys Asn Ala Cys Leu Trp Arg Glu Asn Thr			
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Thr Ser Ser Arg Leu Glu Ala Ile Lys Ile Gln Ile Leu Ser Lys Leu			
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Arg Leu Glu Thr Ala Pro Asn Ile Ser Lys Asp Ala Ile Arg Gln Leu			
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Leu Pro Lys Ala Pro Pro Leu Leu Glu Leu Ile Asp Gln Phe Asp Val
85 90 95

Gln Arg Asp Ala Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
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Ala Arg Thr Glu Thr Val Ile Thr Met Pro Thr Glu Ser Asp Leu Leu
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Thr Gln Val Glu Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser
130 135 140

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165 170 175

Ile Lys Pro Met Lys Asp Gly Thr Arg Tyr Thr Gly Ile Arg Ser Leu
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Lys Leu Asp Met Asn Pro Gly Thr Gly Ile Trp Gln Ser Ile Asp Val
195 200 205

Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
210 215 220

Ile Glu Ile Lys Ala Leu Asp Glu Asn Gly His Asp Leu Ala Val Thr
225 230 235 240

Phe Pro Glu Pro Gly Glu Asp Gly Leu Thr Pro Phe Leu Glu Val Lys
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260 265 270

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Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
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Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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aaa tcc tcc aga ata gaa gcc ata aaa att caa atc ctc agc aaa ctg 192
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 65 70 75 80

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 Leu Pro Lys Ala Pro Pro Leu Gln Glu Leu Ile Asp Gln Tyr Asp Val
 85 90 95

cag agg gac gac agt agc gat ggc tct ttg gaa gac gat gac tat cat 336
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gcc aca acc gag acg att atc aca atg cct acg gag tct gat ttt ctt 384
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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Arg			
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys			
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val			
	275	280	285
gat ttc gaa gct ttt gga tgg gac tgg att ata gca cct aaa aga tac			912
Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr			
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys			
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala			
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Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr			
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Phe Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ala Met Val			
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Arg Leu Glu Gln Ala Pro Asn Ile Ser Arg Asp Val Ile Lys Gln Leu
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Leu Pro Lys Ala Pro Pro Leu Gln Glu Leu Ile Asp Gln Tyr Asp Val
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Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His
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Ala Thr Thr Glu Thr Ile Ile Thr Met Pro Thr Glu Ser Asp Phe Leu
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Val Gln Met Glu Gly Lys Pro Lys Cys Cys Phe Phe Lys Phe Ser Ser
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Lys Thr Val Leu Gln Asn Trp Leu Lys Gln Pro Glu Ser Asn Leu Gly
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Phe Pro Gly Pro Gly Glu Asp Gly Leu Asn Pro Phe Leu Glu Val Arg
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Val Thr Asp Thr Pro Lys Arg Ser Arg Arg Asp Phe Gly Leu Asp Cys
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Asp Glu His Ser Thr Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val
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Asp Phe Glu Ala Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr
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Lys Ala Asn Tyr Cys Ser Gly Glu Cys Glu Phe Val Phe Leu Gln Lys
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Tyr Pro His Thr His Leu Val His Gln Ala Asn Pro Arg Gly Ser Ala
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Gly Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr
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85					90					95						
gtt Val	tta Leu	gga Gly	gat Asp	gac Asp	agt Ser	aag Lys	gat Asp	gga Gly	gct Ala	gtg Val	gaa Glu	gag Glu	gac Asp	gat Asp	gaa Glu	336
100					105					110						
cat His	gcc Ala	acc Thr	aca Thr	gag Glu	acc Thr	atc Ile	atg Met	acc Thr	atg Met	gcc Ala	aca Thr	gaa Glu	cct Pro	gac Asp	ccc Pro	384
115					120					125						
att Ile	gtt Val	caa Gln	gta Val	gat Asp	cgg Arg	aaa Lys	ccg Pro	aag Lys	tgt Cys	tgc Cys	ttt Phe	ttc Phe	tcc Ser	ttc Phe	agt Ser	432
130					135					140						
ccg Pro	aag Lys	atc Ile	caa Gln	gcg Ala	aac Asn	cgg Arg	atc Ile	gta Val	aga Arg	gcg Ala	cag Gln	ctc Leu	tgg Trp	gtt Val	cat His	480
145					150					155					160	
ctg Leu	aga Arg	ccg Pro	gcg Ala	gag Glu	gag Glu	gcg Ala	acc Thr	acc Thr	gtc Val	ttc Phe	tta Leu	cag Gln	ata Ile	tct Ser	cgg Arg	528
165					170					175						
ctg Leu	atg Met	ccc Pro	gtt Val	aag Lys	gac Asp	gga Gly	gga Gly	aga Arg	cac His	cga Arg	ata Ile	cga Arg	tcc Ser	ctg Leu	aaa Lys	576
180					185					190						
atc Ile	gac Asp	gtg Val	aac Asn	gca Ala	gga Gly	gtc Val	acg Thr	tct Ser	tgg Trp	cag Gln	agt Ser	ata Ile	gac Asp	gta Val	aag Lys	624
195					200					205						
cag Gln	gtg Val	ctc Leu	acg Thr	gtg Val	tgg Trp	tta Leu	aaa Lys	caa Gln	ccg Pro	gag Glu	acc Thr	aac Asn	cga Arg	ggc Gly	atc Ile	672
210					215					220						
gag Glu	att Ile	aac Asn	gca Ala	tat Tyr	gac Asp	gcg Ala	aag Lys	gga Gly	aac Asn	gac Asp	ttg Leu	gcc Ala	gtc Val	act Thr	tca Ser	720
225					230					235					240	
acc Thr	gag Glu	act Thr	ggg Gly	gag Glu	gat Asp	gga Gly	ctg Leu	ctc Leu	ccc Pro	ttt Phe	atg Met	gag Glu	gtg Val	aaa Lys	ata Ile	768
245					250					255						
tca Ser	gag Glu	ggc Gly	cca Pro	aaa Lys	cga Arg	atc Ile	cgg Arg	agg Arg	gac Asp	tcc Ser	gga Gly	ctg Leu	gac Asp	tgc Cys	gat Asp	816
260					265					270						

gag aat tcc tca gag tct cgc tgc tgc agg tac cct ctc act gtg gac 864
 Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285
 ttc gag gac ttt ggc tgg gac tgg att att gct cca aaa cgc tat aag 912
 Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300
 gcg aat tac tgt tca gga gaa tgc gac tac atg tac ctg cag aag tat 960
 Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320
 ccc cac acc cat ctg gtg aac aag gcc agt ccg aga gga acg gct ggg 1008
 Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335
 ccc tgc tgc act ccc acc aag atg tct ccc atc aac atg ctt tac ttt 1056
 Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe
 340 345 350
 aac ggc aaa gag cag atc atc tac ggc aag atc cct tcg atg gta gta 1104
 Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365
 gac cgc tgt ggc tgc tca tga 1125
 Asp Arg Cys Gly Cys Ser
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 <212> PRT
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<400> 8

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 Gly Pro Val Gly Tyr Gly Asp Ile Thr Ala His Gln Gln Pro Ser Thr
 20 25 30
 Ala Thr Glu Glu Ser Glu Leu Cys Ser Thr Cys Glu Phe Arg Gln His
 35 40 45
 Ser Lys Leu Met Arg Leu His Ala Ile Lys Ser Gln Ile Leu Ser Lys
 50 55 60
 Leu Arg Leu Lys Gln Ala Pro Asn Ile Ser Arg Asp Val Val Lys Gln
 65 70 75 80
 Leu Leu Pro Lys Ala Pro Pro Leu Gln Gln Leu Leu Asp Gln Tyr Asp
 85 90 95

Val Leu Gly Asp Asp Ser Lys Asp Gly Ala Val Glu Glu Asp Asp Glu
 100 105 110

His Ala Thr Thr Glu Thr Ile Met Thr Met Ala Thr Glu Pro Asp Pro
 115 120 125

Ile Val Gln Val Asp Arg Lys Pro Lys Cys Cys Phe Phe Ser Phe Ser
 130 135 140

Pro Lys Ile Gln Ala Asn Arg Ile Val Arg Ala Gln Leu Trp Val His
 145 150 155 160

Leu Arg Pro Ala Glu Glu Ala Thr Thr Val Phe Leu Gln Ile Ser Arg
 165 170 175

Leu Met Pro Val Lys Asp Gly Gly Arg His Arg Ile Arg Ser Leu Lys
 180 185 190

Ile Asp Val Asn Ala Gly Val Thr Ser Trp Gln Ser Ile Asp Val Lys
 195 200 205

Gln Val Leu Thr Val Trp Leu Lys Gln Pro Glu Thr Asn Arg Gly Ile
 210 215 220

Glu Ile Asn Ala Tyr Asp Ala Lys Gly Asn Asp Leu Ala Val Thr Ser
 225 230 235 240

Thr Glu Thr Gly Glu Asp Gly Leu Leu Pro Phe Met Glu Val Lys Ile
 245 250 255

Ser Glu Gly Pro Lys Arg Ile Arg Arg Asp Ser Gly Leu Asp Cys Asp
 260 265 270

Glu Asn Ser Ser Glu Ser Arg Cys Cys Arg Tyr Pro Leu Thr Val Asp
 275 280 285

Phe Glu Asp Phe Gly Trp Asp Trp Ile Ile Ala Pro Lys Arg Tyr Lys
 290 295 300

Ala Asn Tyr Cys Ser Gly Glu Cys Asp Tyr Met Tyr Leu Gln Lys Tyr
 305 310 315 320

Pro His Thr His Leu Val Asn Lys Ala Ser Pro Arg Gly Thr Ala Gly
 325 330 335

Pro Cys Cys Thr Pro Thr Lys Met Ser Pro Ile Asn Met Leu Tyr Phe

340

345

350

Asn Gly Lys Glu Gln Ile Ile Tyr Gly Lys Ile Pro Ser Met Val Val
 355 360 365

Asp Arg Cys Gly Cys Ser
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 <211> 50
 <212> PRT
 <213> Homo sapiens

<400> 9

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
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<220>
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<400> 10

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Gln Asp Asp Ser Ser Asp Gly Ser
 20 25 30

Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
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<210> 11

<211> 50
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<220>
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<400> 11

Lys Asp Val Ile Arg Gln Leu Leu Pro Lys Ala Pro Pro Leu Arg Glu
 1 5 10 15

Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser
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Leu Glu Asp Asp Asp Tyr His Ala Thr Thr Glu Thr Ile Ile Thr Met
 35 40 45

Pro Thr
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<210> 12
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 <212> PRT
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<400> 12

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 1 5 10 15

Asp Val Gln Arg Asp Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
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Tyr His Ala Thr Thr Glu Thr Ile
 35 40

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Tyr His Ala Thr Thr Glu Thr Ile
 35 40

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 1 5 10 15

Asp Val Gln Arg Ala Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp
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Tyr His Ala Thr Thr Glu Thr Ile
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<210> 15
 <211> 30
 <212> PRT
 <213> Homo sapiens

<400> 15

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 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 16
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<220>
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<400> 16

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 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 17

<211> 30
 <212> PRT
 <213> Artificial sequence

<220>
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<400> 17

Ala Pro Pro Leu Arg Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Ala
 1 5 10 15

Asp Ser Ser Asp Gly Ser Leu Glu Asp Asp Asp Tyr His Ala
 20 25 30

<210> 18
 <211> 20
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<400> 18

Glu Leu Ile Asp Gln Tyr Asp Val Gln Arg Asp Asp Ser Ser Asp Gly
 1 5 10 15

Ser Leu Glu Asp
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<210> 19
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<220>
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<400> 19

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Ser Leu Glu Asp
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Ser Leu Glu Asp
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<211> 10
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<400> 21

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<211> 10
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<220>
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1 5 10